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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/380,704	06/06/2000	ASHLEY I. BUSH	0609.4350001	2953

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	**PAPER NUMBER**
1647	21

DATE MAILED: 08/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Applicati n No. 09/380,704	Applicant(s) BUSH ET AL.	
	Examiner Bridget E. Bunner	Art Unit 1647	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,37,38 and 53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,37,38 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8,10-13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendments of 06 June 2000 (Paper No. 17) and 17 May 2002 (Paper No. 20) have been entered in full. Claims 1 and 37 are amended and claims 3-36, 39-52, and 54-94 are cancelled.

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-2, 37-38, and 53, drawn to a composition for the treatment of conditions caused by amyloidosis and a method of treating amyloidosis in Paper No. 19 (05 March 2002) is acknowledged.

Claims 1-2, 37-38, and 53 are under consideration in the instant application as they read upon the elected metal chelator species of bathocuproine and the elected "additional compound" species of indomethacin.

Sequence Compliance

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). **Specifically, the amino acid sequence disclosed in Figure 6 is not accompanied by the required reference to the relevant sequence identifiers.** This application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825).

Information Disclosure Statement

2. The information disclosure statements filed 14 August 2000 (Paper No. 8), 30 November 2000 (Paper No. 10), 27 December 2000 (Paper No. 11), 16 January 2001 (Paper No. 12), and 15 February 2001 (Paper No. 13) fail to comply with 37 CFR 1.98(a)(2), which requires a legible

copy of each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. *It is noted to Applicant that there is no information disclosure statement present in the application prior to the statement of 14 August 2000.*

Specification

3. The disclosure is objected to because of the following informalities:

3a. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78(a)(2) and (a)(5)).

3b. The Brief Description of Drawings for Figures 19A, 19B, and 19C doesn't seem to match the Figures.

3c. The Brief Description of Drawings does not refer to Figures 19D, 19E, 19F, 26A, 26B, 30A-1, and 30A-2.

3d. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "A COMPOSITION COMPRISING A METAL CHELATOR AND A METHOD OF TREATING AMYLOIDOSIS BY ADMINISTERING THE METAL CHELATOR".

Appropriate correction is required.

Claim Objections

4. Claims 1-2, 37-38, and 53 are objected to because of the following informalities:

Claims 1-2, 37-38, and 53 recite non-elected species.

Appropriate correction is required.

35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-2 and 37-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

6. Specifically, claims 1-2 are directed to a method of treating amyloidosis in a subject comprising administering to said subject an effective amount of (a) the metal chelator, bathocuproine; and (b) one or more pharmaceutically acceptable carriers or diluents; for a time and under conditions to bring about said treatment; and wherein said chelator reduces, inhibits or otherwise interferes with Abeta peptide-mediated production of radical oxygen species. The claims also recite further administering to the subject as effective amount of indomethacin.

The specification teaches that brain tissue is homogenized in water and the specific anti-Aβ monoclonal antibodies are used to assay Aβ extraction by western blot (pg 91, lines 26-28; pg 92, lines 1-2). The specification also teaches that extraction of the same material is repeated with PBS in the presence of cheaters of varying specificities and refers to Table 1. The specification determines that the presence of a chelator increased the amount of Aβ in the soluble extract (pg 92, lines 3-6; Figure 19). Examination of the total amount of protein released by the

treatments reveals that the chelation is not merely liberating more proteins in a non-specific manner (pg 92, lines 14-16). The specification discloses that bathocuproine (BC) exhibits a does-response increase in Aβ extraction from human brain, most likely due to its relatively high specificity for zinc (pg 94, lines 21-25; pg 100, lines 4-7; pg 101, lines 12-14; Figure 25A-25B; Tables 5, 7-8). The specification also teaches that bathocuproine is less effective in extracting Aβ from control tissue than from AD tissue (pg 95, lines 29-30; Figure 20A). However, the specification of the instant application does not teach treating amyloidosis in a subject. The specification does not teach any methods or working examples that indicate administration of bathocuproine or indomethacin/indomethacin to a subject. Undue experimentation would be required of the skilled artisan to determine the optimal quantity of bathocuproine or bathocuproine/indomethacin to be administered to a subject as well as the optimal duration of treatment and route of administration. One skilled in the art would also not be able to predict the effects that bathocuproine or indomethacin/indomethacin might have in a subject since relevant literature reports that the search continues for a treatment that causes the mobilization of amyloid deposits (Gillmore et al. Brit J Haematol 99: 245-256, 1997; pg 249, col 2). Gillmore et al. also indicates that few clinical trials have been performed and the approach to treatment remain somewhat empirical (pg 250, ¶1). Therefore, a large quantity of experimentation would be required of the skilled artisan to treat amyloidosis in a subject by administering bathocuproine or indomethacin/indomethacin.

7. Claims 1-2 and 37-38 are directed to a method of treating amyloidosis in a subject comprising administering to said subject an effective amount of (a) the metal chelator, bathocuproine; and (b) one or more pharmaceutically acceptable carriers or diluents. The claims

are also directed to a pharmaceutical composition comprising (a) the metal chelator, bathocuproine; and (b) one or more pharmaceutically acceptable carriers or diluents. This composition further comprises a compound, indomethacin.

8. As discussed previously, the specification teaches extracting homogenized brain tissue in the presence of bathocuproine. However, the specification does not teach how to use a bathocuproine or indomethacin/indomethacin "pharmaceutical" composition without undue experimentation for the treatment of a disease in an animal. Additionally, the phrase "pharmaceutically acceptable carrier or diluent" in claims 1-2 and 37-38 recites an intended use of bathocuproine or bathocuproine/indomethacin for treatment or administration in an animal. The specification does not teach how to use bathocuproine or bathocuproine/indomethacin without undue experimentation for the treatment of a disease in an animal. (Note, this issue could be overcome by deleting the term "pharmaceutical" or the phrase "pharmaceutically acceptable" from the claims.)

Due to the large quantity of experimentation necessary to determine the quantity of bathocuproine or bathocuproine/indomethacin to be administered, the most effective administration route, and the duration of the treatment, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the effects of the composition *in vivo* (see Gillmore et al.), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-2, 37-38, and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Regarding claims 1-2, 37-38, and 53, the acronyms "Abeta", "TETA", and "TPEN" render the claims vague and indefinite. Abbreviations should be spelled out in all independent claims for clarity.

9. Claims 1-2 are indefinite because the claims do not have a step that clearly relates back to the preamble. For example, there is no step clearly indicating that a metal chelator treats amyloidosis. (This issue could be overcome by amending the last line of claim 1 to recite "...(A-β)-mediated production of radical oxygen species to treat amyloidosis in a subject".)

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sigma Chemical Company (1995; catalog number B 1000; pg 149) in view of Goodman and Gilman (The Pharmacological Basis of Therapeutics, New York: McGraw-Hill, Inc, 1993; pg 5-6).

Sigma teaches the elected species of metal chelator, bathocuproine.

Sigma does not teach bathocuproine in a carrier or diluent. Sigma also does not teach a composition comprising bathocuproine and indomethacin.

Goodman and Gilman teach that the absorption of drugs is dependent upon drug solubility. Goodman and Gilman also teach that drugs given in aqueous solution are more rapidly absorped than those given in oily solution, suspension, or solid form because they mix more readily with the aqueous phase at the absorptive site (pg 5, ¶ 4).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the metal chelator as taught by Sigma by combining it with an aqueous diluent or carrier, as taught by Goodman and Gilman. The person of ordinary skill in the art would have been motivated to make that modification because drugs put into an aqueous solution are more rapidly absorped in a subject. The person of ordinary skill in the art reasonably would have expected success because drugs are frequently put into diluents or carriers. Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Cherny et al. Neuron 30(3) : 665-676, 2001.

Cherny et al. J Struct Biol 130(2-3) : 209-216, 2000.

Kisilevsky et al. Crit Rev Biochem Molec Biol 32(5): 361-404, 1997.

Maury, CP. Lab Invest 72(1): 4-16, 1995.

Gnjec et al. Front Biosci 7 : d1016-1023, 2002.

Fonte et al. J Alzheimer's Dis 3(2) : 209-218, 2001.

Scnabel, J. Science 260 :1719-1720, 1993.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

BEB
Art Unit 1647
August 20, 2002

Gary L. Kunz